Reprinted from BACTERIOLOGICAL REVIEWS
Vol. 21, No. 3, September, 1957
Printed in U.S.A.

VIRUSES, GENES, AND CELLS[1]

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The intimate relationships of viruses and genes have been proper subjects of speculation for many years. More recently, genetic studies, especially on bacteriophages and bacteria have given concrete substance to some of these speculations. For this occasion a brief didactic review of some relevant experimental findings may be appropriate. The support that they can give to concept and methodology in the field of cancer research will be self-evident. More extensive and coherent syntheses of several aspects of virus biology may be found elsewhere (Luria, 1953; Burnet, 1955; Lwoff, 1953; Jacob, 1954; Symposium, 1953; Bertani, 1957; Stent, 1957). The examples arbitrarily selected here will simply reflect my own experience and interests.

MUTATION AND SELECTION

Populations: the first principle of cellular genetics. The unit of experimental manipulation is usually a population of individual cells, and these are the units of growth and genetic change. Much confusion has been generated by such a statement as "the culture developed resistance to this drug," which contains the hidden assumption that the population has reacted as a unit. Mass responses to external agents are indeed known: these are either nonheritable and physiologically reversible, like enzymic adaptation, or cytoplasmic alterations. Heritable adaptation of microbial cultures is usually overgrowth of the population by the fittest cells. However, if the population is not carefully watched, the selective influence may be so subtle, or the overgrowth so rapid, that it will be mistaken for a mass response. A typical example of selective adaptation is the overgrowth of leucine-dependent cultures of neurospora by leucine-independent mutants, in media where leucine is a limiting growth factor (Ryan and Lederberg, 1946). The obvious analogies between neoplasia and growth factor independence require no further comment (Lederberg, 1946), but our knowledge of comparative cell nutrition still falls short of the test.

Mutation. Selective action on a population depends on genetic heterogeneity which, in the last analysis, comes from mutation. With higher organisms, the sporadicity of mutation is no longer seriously questioned. Many investigators have, however, hoped that lacking an insulated germ line, microbial heredity might be more readily influenced. Drug resistance especially seemed to justify this hope in the thinking of many workers. However, a number of examples have been thoroughly studied, and so far there remains no unambiguous demonstration of specific drug-induced mutation, although several claims are still controverted. On the other hand, there are several specific demonstrations of the purely selective action of a drug in the production of resistant populations (Bryson and Szybalski, 1955). This conclusion can hardly be disputed in the face of methods of indirect selection, whereby the resistant clones have never been exposed to the drug (Lederberg and Lederberg, 1952; Cavalli-Sforza and Lederberg, 1956; Sneath, 1955). Law (1954) has analyzed the origin of methopterin-resistant lines of experimental leukemia by related methods, with the same conclusion of a selected change.

The lack of experimental evidence does not, of course, rule out the possibility of the eventual achievement of directed mutation. Rather it speaks for the relative naïveté of our present methods in coping with the sophistication of the developmental pathways between the genes and their end effects. If, as is now doctrinal, genetic specificity depends on the sequence of nucleotides in deoxyribonucleic acid (DNA), a specific mutagenic reagent should discriminate between different nucleotide arrangements. Nothing short

[1] Paper No. 648 of the Department of Genetics. These studies have been aided by grants from the National Cancer Institute (C-2157), Public Health Service and the National Science Foundation.

[2] Eli Lilly & Company Award of the Society of American Bacteriologists, 1953. In its present form, this paper was read at the 11th Annual Symposium on Fundamental Cancer Research, University of Texas Medical Center, Houston, March 9, 1957.

of homologous genetic material is now known to have so nice a preception. However, we may take courage from these bits of knowledge: the second-order specificity of mutagenic and antimutagenic effects, differential inactivation of intracellular components, and the experimental transfer, with functional incorporation, of genetic fragments (transduction).

The point of departure of current studies on chemically induced mutation, mutagenesis, was Auerbach's wartime observations on mustard gases on drosophila (Auerbach, 1951). Since then, a very wide range of compounds has been studied in bacteria and neurospora as well (Giles and Lederberg, 1948; Haddow, 1953; Hemmerly and Demerec, 1955; Jensen *et al.*, 1951). These compounds fall into several groups, principally: highly active organic substituting (alkylating) reagents, such as the mustards, diazomethane, and formaldehyde; peroxides and oxy-free-radical-yielding reagents such as Mn^{++}; and a miscellaneous group, which includes caffeine and other purines, distinguished from the others by low toxicity. The free radicals (·OH, ·OOH) have also been implicated in the mutagenic effects of radiations. By coupling with organic residues, they may also function through alkylation. The mutagenicity of caffeine may be related to natural mutation, because of the occurrence of purines as natural metabolites, and because natural and purine-induced mutation are both depressed by antimutagenic compounds, notably guanosine (Novick and Szilard, 1952).

Like x-rays, the various chemicals are, to a first approximation, indiscriminate in their mutagenic effects.[3] No single locus is uniquely responsive to any one agent, which therefore will give a wide range of different mutants, usually accompanied by a preponderance of unchanged parental cells. Many genetic loci must relate to indispensable functions; their mutations would therefore be lethal. However, specific local damage probably accounts for only a part of the toxicity of mutagens. The compounds are notable for carcinogenic and carcinolytic properties, and we might wish for more precise information on their toxic mechanisms, not to mention their specificity of attack.

The quantitative mutability of different loci varies in spontaneous mutation and as among different mutagens, notwithstanding their qualitative nonspecificity (Giles, 1951; Demerec *et al.*, 1956). The characteristic reactivity of each locus, irrespective of phenotypic effect, should relate to its chemical or structural configuration. In addition, different agents tend to break chromosomes at different places (Kihlman, 1952; Haddow, 1953). The task remains of relating cytogenetic to chemical specificity.

Pyrimidine analogues, such as 5-bromouracil, are incorporated into DNA in place of thymine. Twenty per cent of the thymine in *Escherichia coli* B can be replaced without impairing the viability of the cells (Zamenhof *et al.*, 1956), in contrast to mutation and noninfectivity in substituted phage (Litman and Pardee, 1956). Does the specific replacement in DNA change its function or does bromouracil perturb nucleic acid metabolism more generally (*cf.* Coughlin and Adelberg, 1956)? Nevertheless this replacement is the most tangible remodeling of DNA structure so far achieved.

Disinfection. Some reagents differentially inactivate *plasmids*, leaving the remainder of the cell intact. (*Plasmid* is a generic term for extrachromosomal, intracellular, hereditary factors irrespective of their further identification as plasmagenes, viruses, self-reproductive organelles, endosymbionts, etc., *cf.* Lederberg 1952). This disinfection merges with chemotherapy, insofar as insects can be cured of their endosymbionts by antibiotics—to the detriment of the insect host. Other targets have been the chloroplasts of green plant cells (streptomycin), kappa in paramecium (chloramphenicol), respiratory granules in yeast and parabasal bodies in trypanosomes (acriflavine), and latent viruses in plants (heat).

Local genetic states. Mutation is thought of as an architectural change in a linear chromosome. Its disorder in time and space has tended to disqualify mutation, and nuclear phenomena generally, as elements of cellular differentiation. However, some geneticists are looking to other

[3] Some criticisms of the somatic mutation theory of cancer are based on a misappreciation of the random direction of mutagenesis. The same reagents which induce mutations for biochemical defect are also likely to induce reversions to the normal or a new structure. Mutagenesis is, in effect, the momentary excitation of a chromosomal segment to increase the chance of a new configuration. This is, of course, more likely than not to be an ineffective one.

dimensions of genic change, in the context of "functional states" of the genes. The transposition of heterochromatin or other chromosomal elements can inhibit the action of nearby genes (Lewis, 1950; McClintock, 1956). The change is not permanent, and normal genic function is restored by retransposition of the inhibitory element to a distant site. The action of a chromosome segment can thus be modified without intrinsic structural perturbations. This furnishes an analogical model for alternation of "state" in the salmonella phase variation: here the action of a gene for the flagellar protein switches *on* and *off* without affecting the specificity of the protein made during the *on* phase. For the sake of discussion, the functional states are distinguished from the numerous stable alleles for antigenic specificity (Lederberg and Iino, 1956). So far, we cannot point to any system where, as we may suppose happens in normal development, the switch is controlled from without. However, the *R* gene of maize is heritably modified by passage through a heterozygote with another allele R^{st}. The modified *R* reverts towards the normal state in *RR* homozygotes (Brink, 1956).

Since the transplantation experiments of King and Briggs (1955) point unmistakably to nuclear changes in development, it is just as well that some genetic models are available, rudimentary as they are now.

VIRUSES AND GENES

Recombination. Recombination methodology in bacteria has extended the domain of comparative biology to a group of organisms once thought unique; it has also brought to light virus-gene relationships in a way not yet so practical with other organisms. The classification of bacterial recombination processes is detailed elsewhere (Lederberg, 1955*a*[4]); presently relevant are sexuality and transduction, particularly in *Escherichia coli* and *Salmonella* serotypes.

Sexuality. As originally described in *E. coli* K-12 (Tatum and Lederberg, 1947), sexuality was extremely rare, and selective methods were needed to detect the recombinant clones. For example, two growth-factor-dependent mutants, say a T^- (threonine) and an M^- (methionine), might be mixed and plated on a selective minimal medium on which only T^+ M^+ recombinants would grow. These could therefore be readily detected, even if they constituted only 10^{-6} of the whole population. Subsequently, other fertile strains, an elaborate compatibility system, and a remarkably fertile "Hfr" strain were discovered (Cavalli, Lederberg and Lederberg, 1953) and the cytological basis of recombination observed (Lederberg, 1956*a*). This is a side-by-side pairing or conjugation of intact cells which is accompanied by the transfer of a nucleus from one of the cells to the other, and followed by the separation of the conjugants. By mechanically shearing these pairs, Jacob and Wollman (1956*a*) and Skaar and Garen (1956) interrupted the matings and limited the genetic contribution that segregated to the progeny.[5]

Transduction. This may be defined as the transfer of a genotypic fragment, in contrast to sexuality which involves an intact nucleus. Like any other classification, this one is arbitrary, *e.g.*, a Y-bearing spermatozoon is shy of an intact genome, but the fragments we will have to deal with in transduction are quite small, bearing only one or a very few recognizable markers each. The leading example of transduction is Griffith's (1928) pneumococcus transformation. Unfortunately its genetic interpretation was delayed by the sole use of one marker, the capsular polysaccharide, in all the early work. However, Hotchkiss (1951, 1955) showed that resistance to penicillin, resistance to streptomycin, the capsular character, and other markers, are all transferred independently of one another. The active material has been characterized as bits of DNA, with a molecular weight of several million.

From a genetical viewpoint, these bits are broken fragments of the bacterial chromosomes, which penetrating a new host, can resume their original specific functions after replacing homologous chromosome segments. We do not know whether this requires a material ejection, or whether the new fragment reorients chromosome replication (Lederberg, 1955*a*; Hotchkiss, 1955). The same dilemma, physical breakage *versus* copy choice, pervades modern discussions of crossing-over in higher organisms. It is also un-

[4] Monograph (*Bacterial recombination*) now in manuscript.

[5] Certain technicalities on the interpretation of these findings are still under discussion (Lederberg, 1955*b*) but do not affect the utility of the sexual system for genetic analysis.

known whether the bits are formed by random breakage, during the extraction of the DNA, or whether each bit corresponds to a predetermined unit in the living bacterium.

Transduction can also be mediated by viruses (Zinder and Lederberg, 1952; Lederberg, 1956*b*). In the salmonellae, the phage P22 may be grown on a host, say Gal^+, Xyl^+, M^+ (it really doesn't matter what the symbols stand for, except as genetic qualities, but they are galactose-fermentation, xylose-fermentation, methionine-independence). If this phage is then adsorbed by cells of a complementary genotype, Gal^- Xyl^- M^-, these new types can be detected: Gal^+ Xyl^- M^-, Gal^- Xyl^+ M^-, and Gal^- Xyl^- M^+. That is, a small fraction (about 10^{-5}) of the phage particles carry a Gal^+, or a Xyl^+, or an M^+ gene from the donor bacterium. Of course, this experiment is only feasible when the phage leaves a proportion of survivors. The role of the phage in these experiments is merely as a passive carrier of the genes of the donor cell. The transforming abilities of any phage preparation are strictly determined by the character of the cells on which the phage was most recently grown. A number of salmonella phages have been found to act in the same fashion, as has the phage P1 in *E. coli* (Lennox 1955). Other phages have scarcely been examined for this ability, not to mention viruses for other organisms, where technical problems have still to be overcome.

In salmonella, the transduced genetic fragment, or *exogenote*, is readily separated from the phage nucleus that accompanies it within the same coat. When the phage is treated with x-rays or ultraviolet light, its infectivity may be completely destroyed before the transducing activity is impaired. When a cell is mixedly infected with several phages, one of which is carrying a given exogenote, the transformed clone may become lysogenic for any one of the input phages at random (Zinder, 1955). In certain poorly adapted phage-bacterium combinations, most or all of the transformed clones may remain sensitive or immune to the transducing phage. The envelopment of the exogenote within the phage coat makes it inaccessible to direct chemical analysis at the present time, but DNA-transduction is to phage-transduction as a postcard is to a letter: the message is the same.

Prophage-linked transduction. E. coli strain K-12 is lysogenic for a phage called *lambda*. Unlike the generality of the salmonella and pneumococcus systems, the only markers known to be transduced by *lambda* are a cluster of *Gal* (galactose-fermentation) loci (Morse, Lederberg and Lederberg, 1956*a*, *b*). *Lambda* obtained by ordinary lytic growth is ineffective, and it must be obtained by the UV-induction of lysogenic bacteria. The immediate result of a transduction is often a *heterogenotic* clone, in which the exogenote persists and multiplies side by side with the corresponding homologue from the recipient bacterium. As a further event in these clones, a bacterium may undergo segregation, whereby the exogenote will undergo crossing over with the chromosome, and give rise to any of a variety of recombinant types. (In other cases of transduction, the heterogenotic phase is evidently very brief.) The peculiarities of this system are thought to depend on the linkage of *Gal* to the *lambda* prophage, as will be elaborated shortly.

Lysogeny and lysogenic conversion. The fate of a sensitive bacterium infected with *lambda* is indeterminate: it may lyse and release a crop of progeny phage, or it may survive to give a clone with lysogenic and sensitive components. The lysogenic bacterium is one which proliferates normally, or nearly so, but cells of which may lyse from time to time and release phage.

The sexual recombination system in *E. coli* K-12 has furnished a unique opportunity to study the genetic basis of lysogenicity. Crosses of lysogenic with sensitive strains, and especially the occurrence of diploids which are heterozygous for the trait, showed that the prophage is fixed at a specific bacterial locus, *Lp*, which is linked to another locus, *Gal* (Lederberg and Lederberg, 1953). Lp^+ or the presence of the prophage, can be distinguished from Lp^s, the standard sensitive, by two effects: immunity to the infective virus, and productivity of it, especially upon exposure to UV. If it were not for the latter, the alleles Lp^+/Lp^s could not be distinguished from any other genetic markers in their fundamental behavior.

The hallmark of a virus has been thought to be infectivity, or transmission from cell to cell through the medium. The discovery of transduction has largely obliterated this distinction. In fact, it is appropriate to categorize lysogeny as a kind of transduction, not merely *by* phage, but *of* the prophage. In the *Lp-Gal* system, the prophage is transduced along with the linked

Gal marker. They are readily separated: in fact, from unselected donors, only 10^{-5} of the phage particles preserve the coupling. However, the phage from heterogenotes shows an efficiency of transduction for *Gal* which approaches one. The exogenote here is derived from one previously selected for the coupling of *Gal* and *Lp* in the phage.

The ordering of lysogeny as a subclass of transduction is more than a verbalism. Lennox (1955) and Jacob (1955) have shown that Lp^+, *i.e.*, lysogeny, can be transduced by other phages in linkage with *Gal*. Furthermore, many examples of *lysogenic conversion* have been found in which a bacterial trait is intimately associated with a given prophage, which then serves as a transmissible gene for that trait. Apart from immunity phenomena, which are almost inevitable adaptations to the viral life cycle, specific prophages are associated with toxin synthesis in *Corynebacterium diphtheriae* (Freeman, 1951) and with the somatic antigens in salmonella (Iseki and Sakai, 1953; Uetake *et al.*, 1955). In the latter case, the same phage which is responsible for the conversion also transduces casual fragments at a low efficiency. The lysogenic conversion effect is so inherent in the prophage that it is independent of the immediate donor. This formulation suggests that lysogenic conversion is an extreme case of linkage of bacterial markers to prophage, and predicts that further study should show an occasional separation (*cf.* Terada, 1956).

It must be admitted we do not know the precise mode of association between the prophage and the chromosome. By analogy with other transductions it may be a linear segment, peculiarities such as inducibility being an evolutionary specialization. The same evolutionary argument would allow for other geometries, *e.g.*, a lateral attachment. In any case, the phage nucleus in a lysogenic bacterium (or at least *E. coli*) is a specialized part of the bacterial nucleus.

Host-controlled variations. To this point we have been concerned with the genetic effects of viruses on host cells. Converse effects are also important. For example, an elaborate system of host-controlled variations of phage underlies the typing scheme for *Salmonella typhi*. Phage grown on any given type of host becomes specifically adapted to that host and initially attacks other types very inefficiently. Anderson and Felix (1953) found that the principal determinant of host type is a prophage quite distinct from the Vi_{II} typing phage. These studies, therefore, exemplify lysogenic conversion and host-controlled variation at the same time. Prophage determinants have, in fact, been implicated in most examples of modification. Where they have not been found, *e.g.*, in the modifications of *lambda* (Bertani and Weigle, 1953; E. Lederberg, 1954) the determinant gene might be a mutant prophage (*cf.* Appleyard, 1956; Jacob and Wollman, 1956*b*). As already indicated, we have no operational criterion to argue for or against this origin of a bacterial gene.

A number of more or less remote analogies suggest themselves for the biology of host-controlled variation. Genic modifications were mentioned earlier. In *phenotypic mixing*, two viruses actively growing in the same host jointly determine the phenotype of the protein coats of the progeny phage, regardless of the genotype contained in any single coat (Streisinger, 1956). Transduction exemplifies the incidental carriage of other materials from the host. Finally, there may be obligatory recombination between the host and the phage nuclei in some combinations. Radiobiological studies (Garen and Zinder, 1955) independently suggest that a radiosensitive target occurs both in the host cell and in certain phages. This target must be inactivated in both sites to prevent growth of the phage. Mutations have not been induced by treatment of free virus, but they occur when both the bacterial host and the phage are irradiated (Weigle, 1953), further evidence for a regular mechanism of genetic interchange between the two.

To emphasize the intimacy of virus-host relationships, Luria has spoken of "parasitism at the genetic level." We now have the means to deal with viruses as "genes which function at the parasitic level."

Humility and perspective are necessary ingredients of scientific craftsmanship; here they concur in stressing the far reaches of our ignorance. For technical reasons, bacteria and bacteriophages occupy an active salient. On one flank, they support the inevitable decipherment of genetics as biochemistry. On the other, they have provoked a methodology by which a cellular genetics can be built on the model of the microbes (*cf.* Puck and Fisher, 1956; Lederberg, 1956*c*). The very obscurity of this field at least leaves room for optimism. Nature may

have some surprises in store for us if we but look for exploitable processes of genetic interaction. If this fails, we can still resort to art, for if nuclei can be transplanted (King and Briggs, 1955) why not chromosomes or their parts? In the long run, the genetic bases of the phenotype of neoplastic cells can only be established with the tools of direct genetic analysis—a remark which echoes the state of bacterial genetics just 15 or 20 years ago.

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